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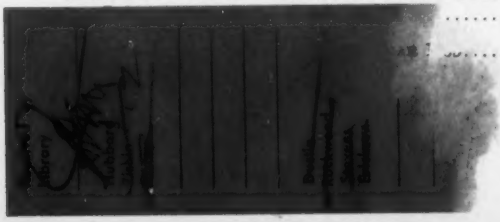

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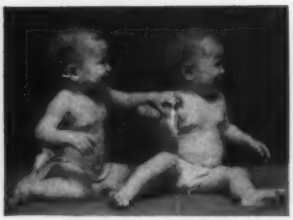

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TURNER'S SYNDROME IN A NEWBORN INFANT

J. William Oberman, M.D.

The following case is an example of the application of recently summarized criteria for the diagnosis of Turner's syndrome in the pre-puberal girl.

CASE REPORT

This 10 month old white female infant was the product of a full-term completely uncomplicated pregnancy. Birth was uneventful and her neonatal condition was excellent; birth weight was 6 pounds, 3 ounces. She was noted to present several congenital abnormalities and was examined completely immediately following birth. There was no familial history of congenital abnormalities. The mother had had one previous stillborn infant. The parents are not related.

Physical examination revealed a small but otherwise well developed, well nourished white female infant who appeared alert and vigorous. Crown-heel length was 19 inches, head circumference 14 inches and chest circumference 13 inches. The most striking physical abnormality was a prominent bilateral soft tissue webbing of the neck. In addition the skin of the nape of the neck was thrown into numerous redundant folds. The head appeared somewhat dolicocephalic but the fontanelles and sutures were normal. The external ears were large and prominent but appeared to be normal otherwise. There was a flattened nasal bridge and bilateral epicanthus. Examination of the oral cavity revealed a highly arched palate. Examination of the chest was normal except that the nipples were very tiny and could scarcely be discerned. Heart and lungs were normal. Abdominal examination revealed no abnormality. The external genitalia appeared to be those of a normal female infant except for the prolapse of a small amount of vaginal mucosa. Femoral pulsations were of good quality. There was marked, non-pitting edema of all four extremities, particularly on the dorsal surfaces of the hands and feet.

At the age of one month, x-rays of the skull, chest, dorsolumbar spine and upper and lower extremities were all normal Bone age was reported as normal. At several months of age, bilateral congenital hip dysplasia was suspected clinically and confirmed roentgenographically, and the child was placed in a Frekas splint. The infant, though small, continued to do very well otherwise although her neuromuscular development was somewhat retarded. Psychological testing at age 9 months revealed a mental age of 4.8 months and an IQ of about 50. At age 10 months she appeared active and alert and was well developed and well nourished. Her weight was 12 pounds 2½ ounces, crown-heel length 25½ inches, head circumference 15⅞ inches and chest circumference 15¾ inches. At this age she was able to roll over but had not yet begun to sit up. She reached for and grasped articles but soon let them drop without further examination. The soft-tissue webbing of the neck, while still present, was less noticeable and the folds of skin at the nape of the neck were less prominent. There was bilateral congenital hip dysplasia, more marked on the right. The non-pitting edema of the extremities, although still prominent, was much less marked than at birth, most of the edema now being confined to the dorsa of the hands and feet. The areas in the upper arms and thighs which were formerly edematous now demonstrated well defined cutis laxa.

At this time the infant continues to do well. She is to be placed in casts for the correction of her hip deformity and will be observed and evaluated periodically.

FIG. 1. Congenital soft-tissue webbing of the neck and edema of the dorsum of the hands and feet.

DISCUSSION

Turner's syndrome was originally described in 1938 by Turner[1] who collected information on a series of young women with congenital webbing of the neck, sexual infantilism and cubitus valgus. The synonym "the syndrome of ovarian agenesis" was later applied to this syndrome since in the majority of these cases diagnostic laparotomy revealed no structure resembling a mature ovary. Instead, the ovaries were represented by glistening white streaks, approximately 3 mm in width located on the posterior surfaces of the broad ligaments and microscopic examination revealed no evidence of germinal epithelium or ovarian follicles[2]. That there was more to this syndrome than the absence of ovaries was indicated by the short stature and the frequent occurrence of other congenital anomalies. Castrated females, for instance, have been shown to be taller than normal, probably from failure of epiphyseal union[3]. Most of the case reports of Turner's syndrome have been by endocrinologists and the

FIG. 2

FIG. 3

FIG. 2. Redundancy of the skin of the nape of the neck and edema of the dorsum of the hands and feet.

FIG. 3. Redundancy of the skin of the nape of the neck.

primary interest has been directed toward investigation of ovarian function. Little attention has been paid to the occurrence of this syndrome in the pediatric age group, case reports occurring only sporadically[3], [4], [5], [6]. Recently, Oberman[7] in an attempt to find criteria for the diagnosis of this interesting condition in the prepuberal female, has reviewed the work of European authors,[8], [9], [10], [11] and has suggested the following diagnostic features:

1. Congenital soft tissue webbing of the neck ("pterygium colli"): This is the most prominent sign of the syndrome. The webbing is bilateral and symmetrical but does not restrict motion of the head in any way. Frequently there is an associated low insertion of the ears.

2. Lymphangiectatic edema of the hands and feet: This is present at birth, is non-pitting, and has been proven by histopathologic investiga-

tion to be due to dilatation of lymphatic capillaries. Resorption of this edema occurs soon after birth and is largely complete by the age of two years.

3. Cutis laxa: Abnormal elasticity of the skin frequently occurs in areas from which the edema has resorbed. This cutis laxa may also be generalized.

4. Dwarfism: This is a constant feature of the syndrome and these children are noted to be short from birth. The reduction in height is proportional and 55 inches is usually the maximum height reached.

5. Mental retardation: This is variable. Certainly many cases do have moderate mental retardation but in any given instance, the intelligence may be average or above average.

6. Epicanthus (bilateral), hypertelorism, highly arched palate: These may be present but are variable findings.

7. Prominent convolutional markings of the skull: An uncommon but extremely interesting x-ray finding. This "digitalization" of the skull mimics that seen in craniostenosis. However, in Turner's syndrome, despite this finding the sutures are not fused and may be readily seen by x-ray.

8. Cardiac anomalies: Coarctation of the aorta is the most common defect found, followed by intraventricular septal defect.

9. Muscle hypoplasia with joint hypermobility.

10. Skeletal anomalies: A wide span, cubitus valgus, pes cavus, minor vertebral chondrodystrophy, Madelung's deformity, fusion of cervical vertebrae, syndactylism, short phalanges, congenital hip dysplasia, mandibular hypoplasia, asymmetry of the skull.

11. Other anomalies: Ocular defects, congenital deafness, renal and pulmonary anomalies.

12. Ovarian agenesis: The effects of gonadal agenesis, of course, do not appear until puberty and so are of little use in the diagnosis of this syndrome in pre-puberal children. These children in adolescence will have primary amenorrhea, mammary hypoplasia with pinpoint nipples, scanty pubic and axillary hair, mild generalized osteoporosis and possibly late epiphyseal union. In addition there is an increased excretion of urinary gonadotropins and diminished excretion of urinary 17 ketosteroids. Ovarian agenesis is not necessarily a cardinal feature of the syndrome, the finding being estimated to occur in approximately one-third of cases[4].

Much attention has been directed recently to the value of skin biopsy in determining the sex of these children and in other children in whom the sex is in question[12]. It has been found that in the female, about 70 per cent of the nuclei of cells in skin biopsy specimens contain a small chromatin body, 1 micron in diameter, usually hemispherical in shape,

pressed against the nuclear membrane, and readily distinguished from the larger nucleolus. This chromatin body has been found to be absent in males except occasionally where chance grouping of chromatin in the nucleus may cause confusion. Other workers[12] have discovered a "female" type of neutrophilic polymorphonuclear cell. Stained smears of the peripheral blood in females have demonstrated small drumstick projections from the nuclei of occasional polys; these are again absent in males. In the hands of experienced investigators, the foregoing are considered to be very reliable. The ultimate answer as to the presence or absence of ovaries, however, rests with the direct visualization of these organs at diagnostic laparotomy. Russell, et al[13] have recently described and contrasted two typical examples of Turner's syndrome. In the first case, nuclei of both skin biopsy cells and peripheral blood polymorphonuclear cells were characteristic of a female. Diagnostic laparotomy revealed bilaterally present ovaries, each having follicular cysts. In the second case, the cell nuclei were characteristic of a male and laparotomy revealed the typical fibrous cords attached to the broad ligaments with no microscopic identification of ovarian tissue.

Once the presence or absence of ovaries has been ascertained, replacement hormonal therapy is possible at puberty[3], [14]. Stilbestrol 0.5–1.0 mg orally may be given daily until the external genitalia have reached adolescent size or endometrial bleeding occurs. Once bleeding has been initiated, therapy is stopped for a week and then restarted for a 2 weeks period. In the 3rd week stilbestrol is continued and progestrone 10–30 mg daily is added. Both drugs are stopped in the 4th week and menstrual bleeding occurs about 2–3 days after cessation of therapy. The regime is then restarted and a normal menstrual cycle established. These "females" of course, are unable to conceive. Some breast enlargement and areolar pigmentation will also develop but mammary size never reaches that attained by normal females. Skjelbred[14] has also suggested the use of 25 mg of testosterone proprionate intramuscularly twice weekly for the first 3 weeks of the menstrual cycle. This has resulted in the development of sexual hair and some increase in height in these adolescents.

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GUILLAIN-BARRE SYNDROME IN CHILDHOOD

Sunday Morning Conference

Harold Stevens, M.D.
James W. Watts, M.D.
Richard H. Todd, M.D.

The following cases of Guillain-Barre syndrome are presented to open a discussion of the diagnosis, differential diagnosis and possible nature of this disorder.

CASE I

W. K., an 11 year old white boy, was admitted to Children's Hospital on October 13, 1954, because of facial paralysis and slurred speech of several days duration. Five days before admission low fever and watery eyes developed; three days before admission lower facial weakness, numbness of his upper lip, slurred speech, "sore neck in the back", and impaired taste sensation developed. However, over this three day period there was no fever, no vomiting, and no pain anywhere except in his neck.

Past and family history were not contributory.

Physical Examination: Temperature was 100°; pulse 88; respirations 20. The boy was alert, cooperative, spoke clearly, and had a clear sensorium. There was paresis of the right lower face; he could barely show his teeth and approximate his lids, and was unable to wrinkle his forehead. He had impaired pain and light touch sensation from his eyes to his chin, but not over his nose. Muscle strength and coordination,

and reflexes were all normal in the extremities. Neurological and general physical examinations were otherwise normal.

Peripheral blood study showed 6 per cent eosinophils with 7,000 leucocytes. Spinal fluid on admission showed 30 leucocytes, (9 per cent polymorphonuclear cells and 91 per cent lymphocytes), 124 mgm per cent protein, 62 mgm per cent sugar, and no growth on culture. Heterophile agglutination on admission was negative.

Improvement was fairly rapid, and by four days after admission, he could wrinkle his forehead and close his eyes fairly well. No specific or symptomatic therapy was used. He was discharged October 19, 1954 with a final diagnosis of Guillain-Barre syndrome.

CASE II

J. K., a 2 year old white boy, was admitted to Children's Hospital on September 24, 1955 because of bilateral ptosis of the eyelids and inability to stand up or sit alone. He had been in another hospital from September 19 to 24 because of these same symptoms. About two weeks prior to admission here the boy had an upper respiratory infection with definite tonsillitis and cervical adenitis which cleared on symptomatic treatment. However, on September 17 he awoke with bilateral ptosis of his eyelids, and later that same day was unable to sit or stand. At the other hospital paresis of the legs was found, along with complete areflexia but no sensory loss; there was a bilateral internal strabismus. A spinal tap on admission there was traumatic but spinal fluid protein was not elevated; a heterophile antibody titer was 1:7. On the third hospital day there, he began to complain of leg pains. It was felt that he had a Guillain-Barre syndrome and on September 24 he was brought to this hospital.

Past and family history were not contributory.

Physical Examination: Temperature was 99.4°; pulse 120; respirations 20. The child appeared acutely ill, was lethargic and irritable and was unable to move his legs. He was unable to sit or stand, and had bilateral ptosis with right internal strabismus. There was generalized hyporeflexia; there was pain but no stiffness on forward flexion of neck; Kernig's sign was positive. The pharynx was injected and there were large posterior and anterior cervical and occipital nodes. On physical and neurological examination otherwise he was normal.

Admission urinalysis, peripheral blood count, tuberculin test (PPD intermediate), and throat culture were all normal. However, the spinal fluid showed 120 mgm per cent protein, 105 mgm per cent sugar, and 11 leucocytes (20 per cent polymorphonuclear cells and 80 per cent lymphocytes). Heterophile agglutination on admission was 1:14. Physical therapy evaluation on the day after admission to Children's Hospital showed severe spasm of back muscles with moderately tight hamstrings; the upper extremities appeared to have fair to good power with full range of motion, and the lower extremities appeared to have fair power although accurate evaluation was impossible because of lack of cooperation.

Penicillin was administered for about three days after admission but no other specific or symptomatic therapy was used except vitamins orally and physiotherapy starting about October 1. A serum potassium on this date was 4.5 meq. per liter. On October 2 a prostigmine test for myasthenia gravis was negative. A heterophile agglutination test on October 3 had a titer of 1:28. Spinal fluid obtained on the fifth hospital day showed 154 mgm per cent protein, 93 mgm per cent sugar, and 2 leucocytes.

Improvement was very gradual and, at the time of this conference, function of his lower extremities is returning; ptosis is somewhat improved; and he can sit alone if

placed in sitting position. He has never had fever. On October 6 the physical therapy department reevaluated his muscle status and found poor to fair strength of all muscles of the legs and of the shoulder girdle with pain on movement.

DISCUSSION

Richard H. Todd, M.D.

I recall the second case vividly; this 2 year old boy was one of the most uncooperative patients we have had for a while. It was very difficult to touch him but whether he had paresthesias or was just abnormally irritable I could not say. Apparently there were no sensory losses so far as the neurologist could find, but when the child was lying flat on his back you could put both of your hands under his lumbar regions without any trouble, so he had much more muscle spasm in the back than Guillian-Barre syndrome cases that I have seen. Many of these cases occur in the polio season so that they must be differentiated from poliomyelitis. However, the symmetry of paresis in this child was against polio; both legs were equally involved, and both eyes seemed to be involved; the fact that his spinal fluid showed few cells with a high protein would make one suspicious of Guillain-Barre syndrome. I think that the chief differential points between the two diseases are the symmetry of the involvement and the high protein with low white count in the spinal fluid in Guillain-Barre syndrome. Another difference usually is that the distal muscle groups are less affected than the proximal muscle groups which was not true in this case where the principal paralysis was in the lower legs. A difference which is only evident after observation is the fact that there is more often complete and rapid recovery from paresis in Guillain-Barre syndrome whereas in polio there is usually some residual. It would be very difficult to reevaluate the muscle strength in this boy unless he cooperated a whole lot better than he did. Now the fact that his heterophile agglutination is going up leads some to believe that this may be a polyneuritis due to infectious mononucleosis; however, with the spinal fluid findings, I would be inclined to go along with the diagnosis of Guillain-Barre syndrome.

James W. Watts, M.D.

I saw the first case in my office and the alternate most likely diagnosis in contrast to the patient Dr. Todd spoke of, was not poliomyelitis primarily, but a probable glioma of the brain stem. His face was almost immobile and in addition to the obvious lag on one side he could not quite close his eyes; when he attempted to squeeze up the eyes the lids were separated by 2 or 3 millimeters, and when he tried to show his teeth there was almost no movement of his face, so one could see there was a bilateral facial paralysis almost complete on one side and partial on the

other side. The rest of the examination was essentially normal and, when we hospitalized him, the examination was exactly the same. A glioma of the pons usually gives no choking of the discs because it affects the cranial nerves before it results in obstruction to the circulation so, although I did not think glioma could be excluded, the onset was almost too rapid for glioma for within five days symmetrical facial paralysis developed with no other cranial nerve involvement. There was no long tract involvement, that is, his reflexes, motor function, and coordination were normal, so my impression was a polyneuritis of the Guillain-Barre type. After the spinal fluid showed elevation of the protein out of proportion to the increase in cell count, my impression was reinforced and I asked Dr. Stevens to see him. Just one further brief comment: one often wonders how far this disease is going to progress and one is always on the spot in making a prognosis. Although the physician does not know how many cranial nerves are going to be involved or to what degree the patient is going to be paralyzed, by watching the chart and the patient he can be just a little bit ahead of the parents.

Harold Stevens, M.D.

I think it appropriate that these cases be presented at these conferences while poliomyelitis is currently frequent if not epidemic. This is one disease that has to be distinguished from poliomyelitis. It is quite apparent that the distinction is more than academic and in recent years it has become particularly important for another reason, namely for the insurance policies, which have been written for poliomyelitis and do not cover Guillain-Barre. Sometimes this causes difficult complications. I suspect that many cases should be labeled poliomyelitis if there is a reasonable doubt rather than deprive the parents of the benefits of an insurance policy or NFIP assistance. At any rate I am sure a great many cases enter the statistics as poliomyelitis but do not belong there. This is one disease that I think is more frequently called poliomyelitis than not.

About two years ago we diagnosed eight cases of Guillain-Barre syndrome in a matter of two months and I think if one looks for it, it can be found. It occurs at all ages, in infancy as well as later childhood. In both of the cases presented the disease is pretty typical. In the first child the prodrome included a low fever and watery eyes. The watery eyes must have been particularly conspicuous to warrant notation and this suggests the possibility that the child had already begun to have facial paralysis; one of the signs of facial palsy is epiphora. The tears are difficult to brush away with the eyelids and what appeared to be increased lacrimation is more than just the usual non-specific response to the fever, which was low, but might reflect a beginning and progressive bilateral facial palsy.

Now it does not state here, but as I recall, a bilateral facial palsy was present. This is quite typical, because Guillain-Barre syndrome often begins with involvement of the cranial nerves and often a facial diplegia. We now know that facial diplegia is just a segment of Guillain-Barre syndrome, but sometimes the disease will not go beyond the facial diplegia. In most instances it moves on to other signs as happened in both cases here. Another point in this case is the mention of impaired sensation which I assumed also reflects cranial nerve involvement, probably of the fifth nerve rather than of the ninth, because there is mention of numbness of the upper lip, so here we have not only a cranial nerve involvement, predominantly facial, but both motor and sensory involvement. This of course is an important point to exclude the diagnosis of poliomyelitis. One of the important distinctions is that although Guillain-Barre is predominantly motor, and sometime exclusively motor, it usually has sensory involvement, both subjective and objective. Subjectively there is pain or paresthesias throughout the limbs, usually in the feet and spreading upwards. On neurological examination there is hypesthesia or hypalgesia. This would of course exclude poliomyelitis. The sore neck and back brings us back again into the common area between poliomyelitis and Guillain-Barre. In Guillain-Barre there is frequently nuchal rigidity. It is not invariable but it is common. Another point is the fever. It mentions low fever here and fever in Guillain-Barre is usually low and there is frequently none at all. This again would help to distinguish it from poliomyelitis. In that same connection the paralysis in Guillain-Barre usually progresses over a longer period than occurs in polio. It may continue for as much as two weeks even in the absence of fever; again in contrast to poliomyelitis. There are some other features which would help to distinguish it. In this child there was a normal white count and the improvement was rapid which is indeed often the case in Guillain-Barre.

Just to extract a few other points on the second case; mention is made of a definite tonsillitis. In the prodromal stage of Guillain-Barre there may be slight fever and upper respiratory infection, abdominal pain or gastro-intestinal complaints. The paralysis then begins anywhere from a couple of days to a couple of weeks later, and again, as here, there is a combination of motor and sensory impairment, paralysis of the legs, areflexia. In this case there was also the characteristic change in the spinal fluid and spasm of the back muscles, again conjuring up the possible diagnosis of poliomyelitis which I feel can be excluded in this instance. The characteristics of this disease include upper respiratory infection with slight fever occurring two weeks to two days before onset of paralysis. When paralysis occurs it is frequently in the cranial nerves and it may be characterized by diplopia, dysphagia or as in this instance, diplegia. The

diplegia is the more common pattern, with or without other cranial nerve involvements. Paralysis can occur in other patterns such as beginning in the feet and extending upward, typical of a Landry's paralysis. The term Landry's is used in a generic broad sense to mean paralysis beginning in the lower extremities spreading upward in a symmetrical pattern. As has already been mentioned, the paralysis in Guillain-Barre is symmetrical; it may begin a little earlier on one side but it is usually on both sides and ascends symmetrically. The sensory involvement may correspondingly increase and ascend in the same order. In Guillain-Barre the proximal muscles are involved more than the distal muscles. The ascending type which may or may not be associated with sensory change may, as Dr. Watts stated, involve the bulb with a fatal outcome but again, contrary to what has been said, many of these cases are fatal. In most instances the outcome is very favorable, but this is not invariable. There have been reports of fatalities running from 8 per cent to 67 per cent. In one series of 15 cases there was 67 per cent fatal outcome. I would guess from my own experience that about 20 per cent end fatally so that the outlook is generally good, but it is a very capricious disease and very difficult and hazardous to predict, even though in the preponderance of cases one would be fairly safe in saying the outlook is good.

After the paralysis reaches a maximum, the patient usually recovers rapidly but there again is a lot of variability. The patient may begin to improve and then level off and remain more or less paralyzed the rest of his life. Improvement may not occur for from three to six months and then progress rapidly. I have seen one case in which there has been a recurrence. This is unusual and very dismaying because we usually assume when improvement occurs that there has already been maximum involvement and that nothing but improvement can occur. Recurrence has been reported by others.

There are several features of the neurological examination that can be mentioned briefly; some have already been stated. Usually there is flaccid paralysis but without fasciculations; the deep tendon reflexes are absent, usually symetrically, again in contrast to poliomyelitis. However, it is possible to have ataxia, in other words cerebellar involvement, and it is also possible to have a pyramidal tract involvement, Babinski signs and spasticity. The sensory examination as mentioned may show hypesthesia, hypalgesia, usually in a symmetrical pattern or in the pattern of peripheral neuritis.

There is one other point that has not been emphasized enough in the literature, and that is the mental signs and symptoms, as noted with this child. He was lethargic and irritable which we could possibly attribute to his hospitalization but in about 10 per cent of cases there are severe

mental changes including psychoses with hallucinations and disorientation.

The laboratory findings are meager. There is no leucocytosis or there may be a relative lymphocytosis in some instances. Bacterial cultures are normal from all sites. The one characteristic laboratory finding is the increased protein in the spinal fluid which has been called albuminocytologic disassociation, a rather formidable name merely meaning that the protein is elevated and the leucocytes are either normal or relatively few. This again is a capricious pattern and it is not always present. For example, cells may be present, sometimes as high as 200, usually lymphocytes. Another variable is that the protein may not rise for a while. It may be as high as 800 milligrams per cent, but is usually around 200 or 300. Various patterns are possible; with the onset of the disease there may be a sudden rise, but usually there is a delay, then a rise, and then a fall of the level of the protein. There have been instances in which the protein has not become elevated for four weeks and then has risen to a high level. There is a temporal variability and you may not catch it at the right point. As you know in late poliomyelitis or recovering poliomyelitis one frequently finds a few lymphocytes and elevated protein; there the spinal fluid findings in the two diseases, late in illness, may be similar. The degree of involvement is not reflected in the spinal fluid protein.

The etiology is unknown. It appears to be viral and certainly is not bacterial but the virus has never been isolated.

The treatment is entirely symptomatic. BAL has been proposed and more recently cortisone, but neither of them is effective. There was one case recently reported of an attack of Gullain-Barre syndrome in an individual who was undergoing treatment for rheumatoid arthritis with cortisone. I think this is a rather devastating argument against its efficacy, and of course in a disease which tends to improve anyway it is awfully hard to evaluate therapy. Occasionally intracranial pressure is sufficiently increased that treatment by decompression is needed. There is sometimes mild retinal congestion and papilledema. There are instances, although very uncommon, in which there is choking of the disk of a remarkable degree and in some rare instances a cranial decompression has been recommended.

Other points in differential diagnosis should be mentioned. Myasthenia gravis was considered in these cases because of the bilateral ptosis, but one does not get sensory involvement in myasthenia gravis nor is spinal fluid protein elevated, and of course the prostigmine response is negative in Guillain-Barre. Tick paralysis should be considered particularly in those cases in which there is a progressive symmetrical generalized motor in-

volvement; that of course is ruled out by the absence of the tick. I think these are the main points to consider in differential diagnosis.

I would estimate that about 20 per cent of cases have residuals, considerably fewer than poliomyelitis and less severe than poliomyelitis; but they occur. We have to keep in mind that many of the reports in the literature reflect hospital cases, in other words, the patient who gets to the hospital is the sicker patient, but we may see mild cases in the home that never get to the hospital. As mentioned, an encephalitic syndrome does occur, I think in somewhere between 10 and 15 per cent of cases. Lead encephalopathy must be excluded. However, in children with lead poisoning the encephalitis would be the dominant pattern which would tend to rule out a Guillain-Barre syndrome and I do not think paralysis would be so generalized in a fullblown Guillain-Barre syndrome. However, the differentiation could be difficult because there is an increased protein in the spinal fluid in lead poisoning; there may be a few cells; there is increased intracranial pressure which can be extremely high with papilledema; and there can be the gastro-intestinal involvement. I think the differentiation might be difficult without the finding of the lead in the urine and the typical red cell stippling and bone changes by x-ray examination. Postdiphtheritic neuritis is distinguished from Guillain-Barre in that diphtheritic neuritis develops much more slowly, but it too is a polyneuritis and it too can give increased protein in the spinal fluid. Probabilities on a statistical basis would favor Guillain-Barre because of the rare occurrence of diphtheria and the frequent occurrence of Guillain-Barre. Guillain-Barre polyneuritis is the commonest polyneuritis, that is, exclusive of that due to alcoholism.

In recent years there have been several well documented reports in which infectious mononucleosis has been present in Guillain-Barre syndrome and the consensus now is that Guillain-Barre syndrome may be due to a variety of causes one of which may be infectious mononucleosis.

Pathological study of nervous system tissue shows a non-specific edema and hyperemia, and in some instances there has been perivascular infiltration of lymphocytes in fatal cases in the cerebrum. In the typical patient who dies from bulbar involvement without encephalitis, the usual pathology is in the peripheral nerve and in the dorsal roots, mainly where the anterior root and the posterior root come together in the spinal cord. There is hyperemia and congestion, myelin degeneration and axis cylinder degeneration. That is the most conspicuous finding. There are cases reported in which there was hyperemia and mild early degeneration in the anterior horn cells, in the sub-cortical nuclei and in the cortex but they were not very striking. The predominant lesion is in the peripheral nerve.

LABORATORY AIDS IN THE DIAGNOSIS OF RHEUMATIC FEVER

Grace H. Guin, M.D.

No laboratory test has been developed as yet which is specific for the diagnosis of rheumatic fever and furthermore, there is no test for rheumatic fever activity that can be relied on when the patient is under full therapy. We will mention just a few of the current tests that are being used and written about in the literature. The *sedimentation rate elevation*, of course, is the most familiar to us all. It is helpful but the limits of normality are not too well defined and that constitutes one of its disadvantages. A perfectly normal person may have an abnormal sedimentation rate for some reason as yet unknown to us. Another disadvantage is that a patient who has rheumatic fever and is on therapy may not reflect the clinical improvement in his sedimentation rate that the physician can observe to be taking place. The white blood cell count is a rather crude, insensitive method but it, of course, has been used.

The demonstration of significant amounts of *serum antibodies to the Streptococcal Group A antigens* has proven to be a valuable tool for the detection of a recent streptococcal infection. The technique of the test consists of the addition of a constant volume of Streptolysin "O" antigen to various dilutions of the patient's serum. After a period of incubation a constant amount of human or rabbit erythrocyte suspension is added and the mixture is reincubated. The antistreptococcal activity is expressed as the reciprocal of the highest dilution of serum that does not show any sign of hemolysis. The normal range is considered to include a titer up to 150 units. A rise in the antistreptolysin titer is usually detectable in rheumatic fever patients in about the second week, and it continues to rise until it reaches its maximum in the third or fourth week. At this point a plateau is reached. The plateau lasts frequently for months and this is one of the disadvantages, as it does not reflect any improvement the patient might make. After a few months the plateau begins to fall and the rate of fall from the plateau is as a rule slower than the rate of increase. The advantage of the antistreptolysin titer is its specificity for the streptococci; cross reactions from antibodies formed by other bacteria do not really present a significant problem in the interpretation of this test. Nonstreptococcal diseases as a rule do not give a rise in antistreptolysin titer. The work that has been done shows between 80 and 90 per cent of patients with rheumatic fever will have a rise in the titer. This does not mean that from 10 to 20 per cent of cases of rheumatic fever are not associated with the streptococcal infection since we know that an even larger portion of patients with a proven streptococcal infection may not necessarily develop this particular antibody and this very fact defines one of the

limitations of this test. The absence of a significant rise in this titer because of its specificity does not exclude the possibility of a recent streptococcal infection or rheumatic fever. But the antibody response occurs in such a high proportion of cases of rheumatic fever that the finding of a low or negative titer in the early phases of a disease believed to be rheumatic fever should lead to reevaluation of the diagnosis. It is possible for a patient with a disease simulating rheumatic fever to have a high antistreptolysin titer from a recent streptococcal infection that is not related to rheumatic fever. This is more likely, however, to be encountered in epidemics where there is streptococcal infection and as a rule this has been rather rare. The effect of antibiotic therapy suppresses antibody response to a number of the streptococcal antigens. Adequate antibiotic therapy does not consistently remove the streptococcus from the throat nor does it cause complete suppression of antibody formation.

Another test that we frequently use is the *C-reactive protein* which is not diagnostic but will give an extremely sensitive measure of the presence and degree of an inflammatory process. This, in contrast to the antistreptolysin test, is non specific. C-reactive protein is a protein that appears in the blood when there has been tissue destruction or where there is inflammation. It may occur in acute coronary disease or in many types of infections. The test is simple, and easy to perform. A small amount of the patient's serum is added to the rabbit antiserum and the precipitation which forms is allowed to settle. Readings are made by measuring the height of the column of precipitate against a millimeter scale. Readings may be evaluated as follows:

A. No visible reaction as 0.
B. Slight to strong reaction from 1 mm. to 6 mm. of precipitate as 1+ to 6+.
C. Any precipitate over 6 mm is recorded as 6+.

Application has shown that this test is not reliable in "pure" chorea. C-reactive protein is nearly always absent although it does appear in the active phases of rheumatic fever and as a rule is roughly proportional to the severity of the disease.

Acute phase reactants is a term that designates substances in the serum whose levels are characteristically altered in the presence of an acute disease. For instance, the concentration of *mucoproteins* in the serum is increased in patients with rheumatic fever and a return to normal is consistent with an inactive state of the disease. Patients with Sydenham's chorea generally have normal concentrations of mucoprotein. Although well correlated with the sedimentation rate, the mucoproteins do lag behind the sedimentation rate, the change in the sedimentation rate ap-

pearing first. In patients who respond when treated with ACTH, the mucoprotein level begins to return to normal along with subsidence of the clinical disease.

Hyaluronidase is one of the products of the streptococcus hemolyticus. The possible role of this enzyme in the pathogenesis of rheumatic fever has been the subject of recent speculation based on the fact that rheumatic fever is a disease of the hyaline connective tissue, and that hyaluronic acid which characterizes hyaline is digested or depolymerized by hyaluronidase. A study was done in which *antihyaluronidase* titer was measured against the fractionated streptococcus to determine which of the antigens of the streptococcus was the most active in this disease process. Fractionated streptococcus has been found to be composed of three parts, the cell wall, the CP or the cytoplasmic particles, and the S or the supernatant protein particles which are believed to be the nucleus, if the streptococcus has such. The titers of antihyaluronidase against antigens of the cytoplasm and the nucleus were measured; they rose in the active phase and fell with the inactive phase, correlating with the severity of clinical disease.

To continue with the acute phase reactants, the *serum nonglucosamine polysaccharides* are normal polymers of different carbohydrate complexes present in both the albumin and the globulin fraction of serum and these are increased in many diseases such as tuberculosis, and other bacterial infections. Since that was so, studies were carried out to see if there was any alteration in the nonglucosamine polysaccharides in the presence of rheumatic fever and it was found in one series that the serum levels of these substances were elevated in every individual that had rheumatic fever in the active phase with the exception of one patient with Sydenham's chorea and one patient with active lipoid nephrosis. Many, but not all, of the patients with inactive rheumatic fever responded with an elevation in the nonglucosamine polysaccharide and it was decided that this test was of limited value in diagnosing active rheumatic fever.

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EDITORIAL

ASEPTIC MENINGITIS VERSUS POLIO: WHO PAYS?

Dr. Stevens' discussion of Guillain-Barre syndrome in this issue emphasizes again how little is known of the etiology of non-bacterial meningoencephalitis: "a great many cases of spinal fluid disease enter the statistics

as poliomyelitis but do not belong there", and "many cases should be labeled poliomyelitis if there is a reasonable doubt rather than deprive the parents of the benefits of an insurance policy or NFIP assistance". At first reading these two statements may seem directly opposed; in fact they merely represent the difference between scientific certainty and clinical presumption; and usually clinical presumption takes precedence in reporting disease when scientific proof is lacking. There are, of course, obvious objections to this position: 1) medical records and statistics lose certain validity; and 2) the edge of objectivity in reporting tends to be dulled if economics play a role in influencing "reasonable doubt" toward the diagnosis of poliomyelitis.

It appears that a solution to this problem is brewing in research virus laboratories: Studies in the past decade indicate that 25 to 60 per cent of patients with non-paralytic, non-bacterial meningitis may be infected with (any of) poliomyelitis, mumps, lymphocytic choriomeningitis or herpes simplex viruses or leptospira. In addition large numbers of presently untypable enteric or "orphan" (ECHO) viruses are currently being isolated from poliomyelitis like disease. For example, in a survey of fecal samples from "poliomyelitis" patients at Children's Hospital during the 1952 season, Shelakov and Habel found that of all viruses isolated from patients with "non-paralytic poliomyelitis" 39 per cent were poliomyelitis virus; the others were not typable with known poliomyelitis strains. At the present time it appears that a majority of these are group B Coxsackie viruses. Similar findings are being noted in other virus laboratories.

As diagnostic procedures for all of these agents are improved, presumably specific diagnosis will become more practical and less expensive. For the time being, however, unless the tests are done on a research basis, the cost of viral diagnostic procedures is prohibitive. For example, from a fee schedule recently proposed by a commercial virus diagnostic laboratory, it could cost the patient as much as $47.50 completely to document a case of poliomyelitis. It is unlikely that physicians or patients will accept such fees readily, especially if the procedures also introduce the likelihood of eliminating a "reasonable doubt" which qualifies them for financial assistance under an insurance plan or NFIP aid.

Until the costs become more realistic, one possibility would be for the insurance companies and NFIP to underwrite the cost of viral diagnostic facilities in certain centers. This would in the long run save them money; statistics would improve; and scientific objectivity in disease reporting would be insured.

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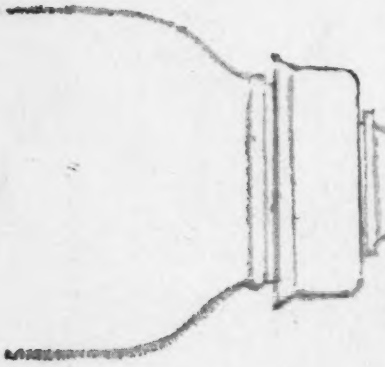

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